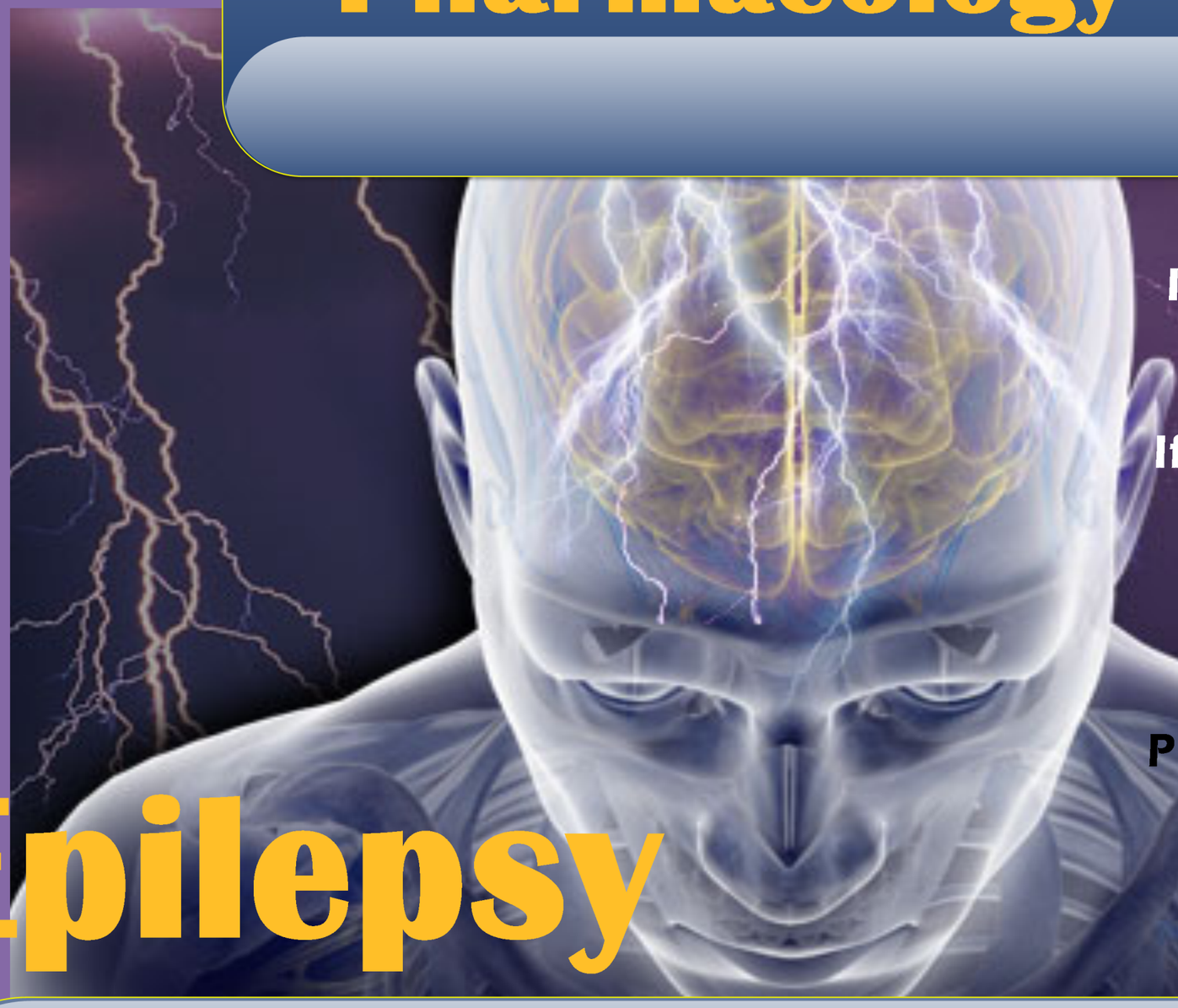
Draw Pharmacology in your mind



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If you are postgraduate and want to revise pharmacology by an easy way
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لا تنسونى من صالح دعائكم

Epilepsy

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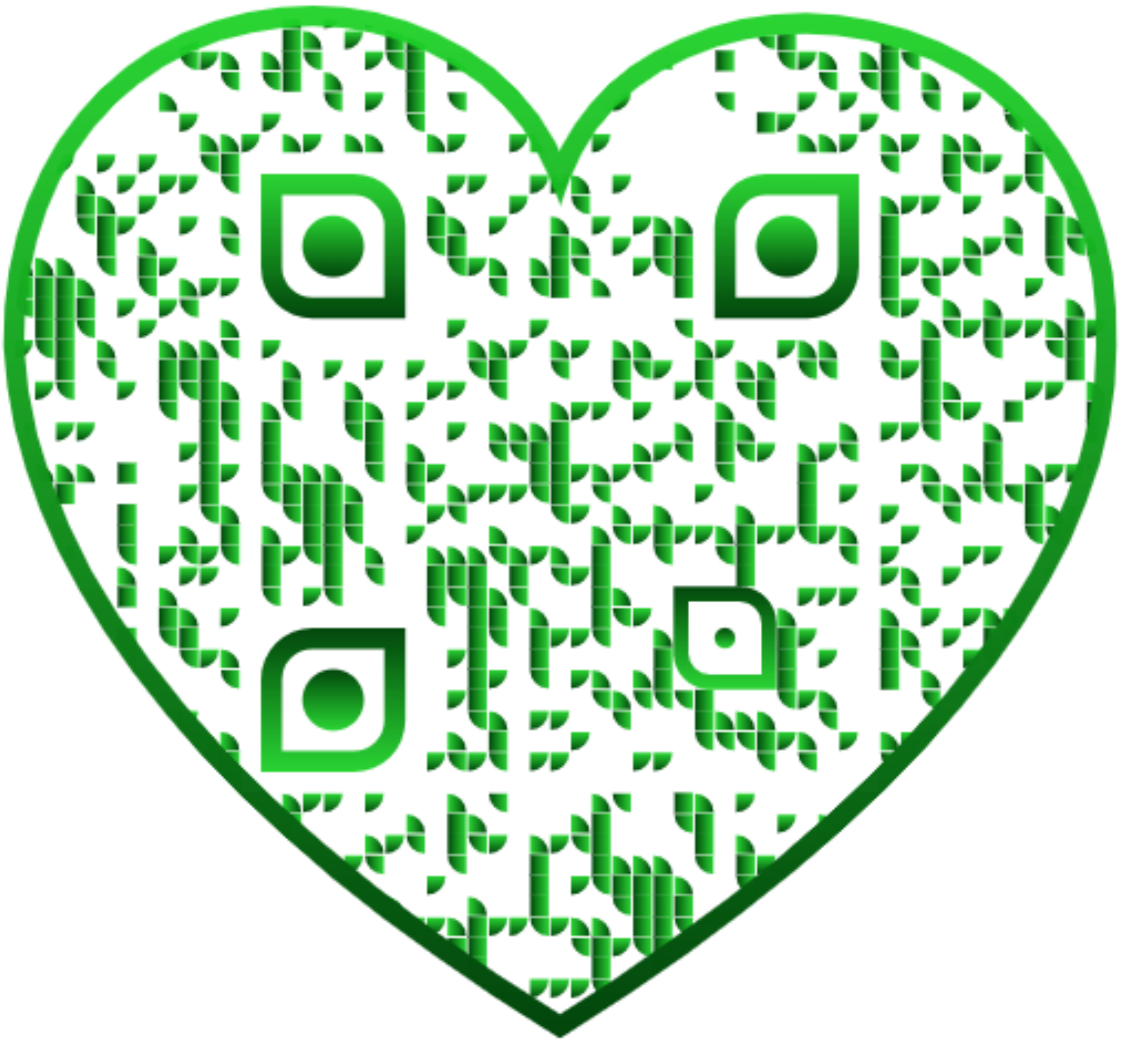


Epilepsy

A group of **chronic** CNS disorders having in common the occurrence of sudden transient episodes (seizures) of:
1. Abnormal autonomic activity
2. Abnormal motor activity (convulsions)
3. Abnormal psychic activity

Etiology

◆ Epilepsy results from abnormal firing of a small population of neurons in some specific areas in brain → abnormal excitability → they are called **"primary focus"** or **"focal area"**
⊗ If the focal area is located in a **motor area** → epileptic seizures include **convulsions**
⊗ If located in a **parietal cortex** → seizures include **visual, auditory or olfactory hallucinations**

Classification

1. According to the cause

Primary epilepsy

◆ **No** anatomical cause, in newborn → brain malformations → lack or low oxygen during delivery
◆ Patient receives a **life-long** treatment

Secondary epilepsy

◆ There is an **anatomical cause** ***(ex.****trauma, Fever, Hypoglycemia, Meningeal infection)*
◆ Patient is treated **until** the cause is corrected

2. According to characteristics

Partial epilepsy

1. Simple

◆ The muscular activity is **limited to the same side** of the body and spread in an **orderly way** → **ex.** *when convulsions begin in* fingers → hand → arm → leg → foot *(all at the same side)*
◆ Patient is **conscious** during seizures ***(awareness is retained)***

2. Complex

◆ **Associated with**
1. Impaired consciousness ***(awareness is lost)***
2. Confused behavior
3. Loss of contact with environment (ex. can not even reply when someone talks to him)

- Affects *small portion* of the brain
- May progress to more complicated type *(ex. Generalized tonic-clonic seizures)*

Generalized epilepsy

◆ **Characterized by**
1. Sensory **aura** (before the attack, the patient smells, sees or hears differently)
2. **Loss of consciousness**
3. Tonic contraction of all body muscles (muscle stiffness & rigidity)
4. Clonic spasm (repetitive jerking movements)
5. **Post-ectus sleep** (the patient sleeps after the attack)

3. Tonic-Clonic (Grand-mal)

- Begin as *focal seizures* (locally) **then** they spread *to both hemispheres* of the brain leading to abnormal electrical discharge
- May be convulsive or non-convulsive *(hallucinations as we said)*
- Immediate loss of consciousness
- The **attack** is very evident on EEG *(electroencephalogram)*

4. Absence (Petit-mal)

◆ Occurs mostly in **children** **4-12 years old**
◆ **Characterized by:** Sudden immobility - Vacant look in the eye - Eye-lid blinking
◆ Episode lasts for **30-60 seconds** / **more than 1** episode per day

5. Myoclonic

◆ **2ry epilepsy** occurs due to: Encephalitis - Drug poisoning - Uremia
◆ **Characterized by:** **Short episodes** of muscle contraction known as **"intermittent clonic jerks"**

6. Fibrile seizures

2ry epilepsy occurs due to: **Fever** in **children** **(3 months to 5 years old)**

7. Status epilepticus

Successive paroxysms نوبات متعاقبة of **tonic-clonic convulsions**
So, it is a **severe, life-threatening** form of epilepsy → **emergency case**

Theories

◆ The initiation of epileptic attack begins from nerve cells in a **focal area**
◆ Those nerve cells differ from other nerve cells in their **unstable resting membrane potential**
◆ The **balance** between the excitatory neurotransmitter **"Glutamate"** and the inhibitory neurotransmitter **"GABA"** is **impaired** in the focal area

So treatment !

1. Drugs stabilizing neuronal resting potential → *they modify ionic conductance in nerve cells by:*
- Interfering with voltage-gated Na^+ channels
ex. Phenytoin, Carbamazepine, Sodium valproate
- Interfering with Ca^{+2} channels
ex. Ethosuximide
2. Drugs ⇑ the effect of GABA
ex. Phenobarbital, Benzodiazepines, Gabapentine, Vigabatrin, Tiagabine, Progabide
3. Drugs ⇓ the effect of Glutamate
ex. Felbamate

Antiepileptics

1. Phenytoin

Mechanism

1. It partially blocks Na^+ channels leading to:
• Prolongation of refractory period
• ⇓ excitability of the membrane
• ⇑ the threshold of excitation
→ so it is a **membrane stabilizer**
2. It also
• ⇓ Ca^{+2} influx during depolarization
• ⇓ Glutamate release

Kinetics

• **Absorbed orally** and **extensively metabolized by liver** by **saturation kinetics** *(the molecules of the drug saturates the binding sites of the enzyme)* → so, the next doses will have longer half-life than the first one → may lead to toxicity if not well monitored
• **Dose** → once daily

Drug-Drug interaction

1. As it is **extensively metabolized** by liver → so it will be **affected by LME inducers and inhibitors**
2. As it is **LME inducer** → it will affect drugs metabolized by LME
ex. Praziquantel
3. It is **highly protein bound** → so will compete with drugs bound to plasma proteins
ex. Valproate *(LME inhibitor, Displaces phenytoin from plasma proteins)*

Uses

• **All forms of epilepsy** **except** **"Absense seizures"** *(may worsen the case)*
• **Trigeminal neuralgia**

Adverse effects

1. Depression of CNS leading to **Nystagmus** تأرجح العين and **Ataxia**
2. GIT disturbances due to the alkalinity of the drug

Antiepileptics

6. Benzodiazepines

Mechanism

- They bind to $GABA_A$ receptors at the **BDZs binding site** → so ⇑ affinity of GABA to its receptor sites **causing:**
1. **More frequent opening of Cl^- channels**
2. **Hyperpolarization** and inhibition of neuronal activity

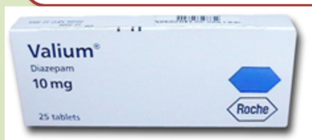
Uses

Clonazepam

As maintenance therapy in:
1. Myoclonic epilepsy
2. Febrile seizures
3. Status epilepticus

Diazepam

Rectally as prophylaxis in Febrile seizures



Examples

Diazepam - Clonazepam - Nitrozepam - Lorazepam
(long acting types)

Notes

1. The antiepileptic dose of BDZs and Phenobarbital < their doses used as anxiolytics
2. **Lorazepam** has shorter pharmakokinetic half-life but stays in the brain longer than diazepam

2. Carbamazepine

Mechanism

Blocks Na+ channel
(Continue)

Kinetics

1. **Metabolized** by liver
2. **Initial** half-life is **25-60 hours**, it decrease upon prolonged use to reach **10 hours** due to its **LME inducing effect**
3. **Dose:** Given orally twice daily by a slow increase in the dose **(titration)** till the seizures are controlled (should be monitored)

Uses

- **All forms of epilepsy**
- **Trigeminal neuralgia**
- **In manic-depressive illness**

Remember we said before 2 types of treatments for manic-depressive illness
Li salts , Aripeprazole

Oxcarbazepine (Trileptal®)
a modified carbamazepine
Better kinetics

5. Phenobarbital

Mechanism

Increase binding of GABA to $GABA_A$ receptors *promote its inhibitory effect*

Uses

2nd line therapy in **Febrile convulsions and status epilepticus** (IV)

4. Ethusoximide

Mechanism

Blocks T-type Ca^{+2} channel preventing the propagation of abnormal electrical discharge

Kinetics

Taken orally once daily due to long half-life

Uses

- **Drug of choice for absence seizures**
- ***Notice ..*** *Its use is **limited** due to its very **narrow spectrum***

3. Sodium valproate

Mechanism

1. **Blocks Na^+ channel**
(Continue)
2. ⇑ GABA action

Uses

1. **The most effective agent in myoclonic seizures**
2. **Absense seizures**
3. **Tonic-clonic convulsions**

Antiepileptics

Remember we said before 3 types of treatments for manic-depressive illness
Li salts , Aripeprazole, Carbamazepine

14. Lamotrigine

Uses

1. Effective in a wide variety of seizures including partial seizures, generalized seizures, typical absence seizures and the Lennox-Gastaut syndrome
2. It is also approved for use in **bi-polar depression**

Mechanism

Blocks **Na^+** channels as well as high voltage-dependent **Ca^{+2}** channels

Kinetics

Its half-life (35 hours) → decreased by LME inducers *(**ex.** Phenytoin and Carbamazepine)* and increased by greater than 50% with addition of *Valproate* → so Lamotrigine dose should be reduced when using valproate, unless the Valproate is being used in small dose to provide a boost to the Lamotrigine serum concentration

Adverse effects

Rapid titration to high serum concentration of Lamotrigine have been reported to cause **rash** which in some patients *may progress to a serious life-threatening reaction*

13. Topiramate

- Derived from D-fructose
- Has complex long lasting anticonvulsant action that cooperate to limit the spread of seizure activity

Uses

It is effective in **partial seizures** and as an **add-on in Lennox-Gastaut syndrome**

7. Vigabatrin

Mechanism

- **Irriversible inhibition of GABA transaminase** *(which bread down GABA)* → so ⇑ GABA concentration in the brain
- **Note that..** it is structurally similar to GABA so can bind to the enzyme

Uses

Treatment of epilepsy **uncontrolled** by other drugs

12. Clomethiazole

It is effective in controlling *status epilepticus*, but it used mainly to treat agitated states specially **alcohol withdrawal**

8. Tiagabine

Mechanism

Inhibition of **GABA reuptake** → by **irreversible inhibition of GABA transporter** (GAT-1)

Uses

2nd line drug in partial or secondary generalized seizures

11. Felbamate

Mechanism

1. Blocks NMDA receptors → preventing the entry of Na^+ and Ca^{+2} from the ion channels linked to NMDA receptors *(this channel is blocked by Mg^{+2} in resting state)*
2. Block voltage gated Ca^{+2} channels
3. Modulate Na^+ channels conductance

Adverse effects

Aplastic anaemia and liver failure so its use is limited now

9. Progabide

GABA mimetic drug

10. Gabapentin

Mechanism

It is thought that **it ⇑ utilization of Glutamate →** so may augment the availability of Glutamate as a precursor in GABA synthesis

Kinetics

It does not bind to plasma proteins, excreted unchanged through the kidneys dose adjustment must be done for renal diseased patients